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Matrix metalloproteinase 2 expression and disease-free survival of patients with osteosarcoma: a meta-analysis.

Tianshu Gao, Zhenting Wang, and Yi Liu

Department of Orthopedics, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu Province, China.

Keywords: meta-analysis; MMP-2; osteosarcoma; prognosis.

Abstract. Numerous studies indicate the influence of matrix metalloproteinase-2 (MMP-2) overexpression in osteosarcoma (OS) outcomes. A previous study has systematically analyzed the correlation between MMP-2 expression and the prognosis of OS. However, the results of subsequent studies remain inconsistent. Therefore, a meta-analysis in terms of the prognostic value of MMP-2 expression in OS was conducted. We employed the Newcastle-Ottawa scale (NOS) to evaluate the quality of the studies. Five studies involving 284 patients were included. The relative risk (RR) with a corresponding 95% confidence interval (95%CI) was calculated to appraise the predictive value of MMP-2 positive expression for OS recurrence and metastasis, and lower disease-free survival. It was indicated by the results that MMP-2 positive individuals with OS had higher recurrence and metastasis rates than negative individuals (RR=1.85, 95%CI:1.16-2.93, $p<0.01$). Sensitivity analysis showed that the combined RR was stable. There was no significant change, independently of whichever article was excluded.

Corresponding author: Yi Liu. Department of Orthopedics, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu Province, China. Email: liuyiwph@nau-edu.cn

Expresión de la metaloproteinasa de matriz 2 y supervivencia libre de enfermedad de pacientes con osteosarcoma: un metanálisis

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Palabras clave: metanálisis; MMP-2; osteosaroma; pronóstico.

Resumen. Numerosos estudios indican la influencia de la sobreexpresión de la metaloproteinasa-2 de matriz (MMP-2) en los resultados del osteosarcoma (OS). En un estudio previo se analizó sistemáticamente la correlación entre la expresión de MMP-2 y el pronóstico del OS. Sin embargo, los resultados de estudios posteriores siguen siendo inconsistentes. Por lo tanto, se llevó a cabo un metanálisis en términos del valor pronóstico de la expresión de MMP-2 en el OS. Se empleó la escala de Newcastle-Ottawa (NOS) para evaluar la calidad de los estudios. Se incluyeron 5 estudios con 284 pacientes y se calculó el riesgo relativo (RR) con su correspondiente intervalo de confianza del 95% (ic95%) para evaluar el valor predictivo de la expresión positiva de MMP-2 para recidiva de OS y metástasis, y menor supervivencia libre de enfermedad. Los resultados indicaron que los individuos positivos para MMP-2 con OS presentaron mayor tasa de recidiva y metástasis que los individuos negativos (RR= 1,85; ic 95%: 1,16-2,93; p<0,01). El análisis de sensibilidad mostró que el RR combinado era estable. Cualquiera que fuera el artículo excluido, no hubo ningún cambio significativo.

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INTRODUCTION

Osteosarcoma (OS) is one of the most common primary malignant bone tumors, which mainly afflicts children, adolescents, and young adults. The incidence rate of OS worldwide is 1 to 3 per million people every yea [1,2]. Owing to advanced surgical procedures and combined chemotherapy, the survival rate of OS sufferers has improved from under 20% to 70% [3]. Nevertheless, this improvement was limited to individuals with local or earlier-stage OS, and the survival rate of individuals with recurrences or metastasis has not improved [4]. At present, the pathogenesis of OS remains ambiguous [5]. Considering there is no suitable biomarker to estimate the prognosis of OS, it is crucial to find an appropriate biomarker to identify those critical patients and give them individualized treatment on time.

Matrix metalloproteinases-2 (MMP-2) pertains to the family of zinc-dependent endopeptidases. It is associated with diverse cytological processes, including cell proliferation, migration, apoptosis, angiogenesis, and immunity [6]. Previous studies have shown its overexpression in endometrial, oral epithelial, and hepatocellular carcinoma and generally predicted poorer prognosis [7-9]. MMP-2 may also be related to the prognosis of OS sufferers, but the conclusions remain

controversial [10-14]. Therefore, we performed a meta-analysis to systematically evaluate the correlation between the expression of MMP-2 and OS recurrence and metastasis.

MATERIALS AND METHODS

Search strategy

A systematic search was performed in PubMed, Embase, Cochrane Library, Wanfang database and China National Knowledge Internet (CNKI) for relevant articles that were published before February 9, 2021 with no language restrictions. These terms were included: "osteosarcoma" or "osteogenic sarcoma" and "matrix metalloproteinase 2" or "MMP-2". The ethics approval is inappropriate because meta-analysis is based on former studies.

Inclusive and exclusive criteria

Inclusive criteria:

1. MMP-2 expression in OS tissues was determined by immunohistochemical staining;
2. Patients were pathologically diagnosed with OS (gold standard);
3. Included studies had to be cohort studies;
4. Sufficient information for constructing a 2×2 contingency table was available in these studies.

Exclusive criteria:

1. No pathology was applied to confirm the diagnosis of OS;
2. The critical value for positive versus negative expression was not given;
3. Review articles, case reports, dissertations, and articles on in vitro cell experiments and animal experiments.
4. MMP-2 expression was not recorded with dichotomous variables, or the patient survival outcomes were unidentified.
5. Earlier and smaller sample size studies were excluded for articles with the same patient population from the same authors.

Data extraction

Two investigators (TG and ZW) extracted the data separately from selected articles. Two investigators (YL and TG) reached a consensus and then crosschecked the data extracted. The main information extracted from the ultimately selected studies is presented below, including the first author's name, publication year, number of participants, and the critical value. MMP-2 expression was divided into positive and negative groups according to the critical values provided in the articles.

Quality assessment

Newcastle-Ottawa scale (NOS) [15] was employed to evaluate the quality of the studies. NOS possesses eight indicators with a total of nine stars. Studies obtaining a score of no less than six stars were included.

Statistical analysis

The pooled risk ratio (RR) with 95% confidence intervals (95%CI) was calculated to evaluate the predictive value of MMP-2 expression for OS recurrence and metastasis. The significance of the pooled RR was then checked through the Z test, which was considered significant when the P value was <0.05. The heterogeneity between the studies was evaluated through I^2 statistics, which described the proportion of total variation in meta-analysis assessment from 0 to 100%. The random effect model was used in this meta-analysis. We also adopted Begg's funnel plot together with Egger's test to evaluate the probability of publication bias. The statistical analysis was performed by The Review Manager 5.3 (RevMan 5.3) and Stata version 12.0 (Stata Corporation) softwares. The 2-tailed P value under 0.05 would be considered statistically significant.

RESULTS

Selection and study characteristics

Five cohort studies [10-14] with 284 individuals were included in the primary retriev-

al and ulterior evaluation of full texts (Fig. 1). Two of them were written in English, and the other three were written in Chinese. Among the 284 individuals, 191(67.3%) individuals were positive for MMP-2 expression, and 93(32.7%) individuals were negative for MMP-2 expression. The other study characteristics are shown in Table 1.

Quality assessment of studies

We evaluated the quality of the included cohort studies through the NOS. The scores ranged from 6 to 8 stars, with an average score of 6.6 stars. The characteristics of the included studies are shown in Table 1, and the detailed scores for each study are listed in Table 2.

Meta-analysis

The combined RR for evaluating the correlation between positive MMP-2 expression and OS recurrence and metastasis is (RR=1.85, 95%CI:1.16-2.93, p<0.01) (Fig. 2). This also indicated that removing any separate study did not significantly change our results. The Begg funnel plot and Egger's test assessed the publication bias. The funnel plot suggested that there was no obvious publication bias in this meta-analysis (Fig. 3), and the same outcome was obtained by the Egger's test (p>0.1).

DISCUSSION

OS is one kind of primary bone tumor mainly afflicting the young generation [16,17]. The survival rate of local or earlier-stage OS patients has increased by over 70% owing to advanced surgical techniques and combined chemotherapy. Still, the prognosis of patients with recurrence or metastasis remains tragic [18]. Therefore, it is vital to identify high-risk patients through appropriate biomarkers and give them individualized treatment as soon as possible.

Belonging to the zinc-dependent endopeptidase, MMP-2 hydrolyzes diverse molecules in the extracellular matrix. For example, it participates in numerous biological processes, including cell proliferation, differentiation, adhesion, and migration. Its overexpression is usually associated with

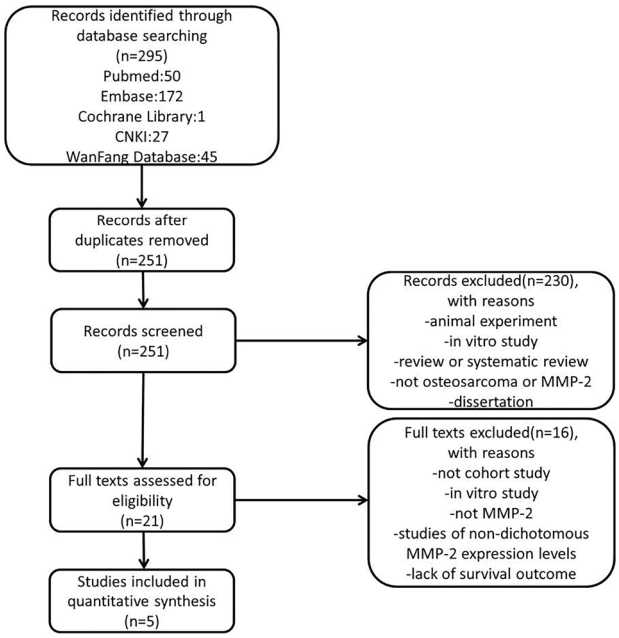

Fig. 1. Schematic representation of the study selection.

Table 1

Characteristics of included studies and NOS scores.

Reference	Study	Year	No. of individuals	Average age (y)	Average follow-up period (m)	Critical value	MMP-2 positive		MMP-2 negative		NOS score
							Recurrence or metastasis	Total	Recurrence or metastasis	Total	
[10]	Gong 2020	2020	73	23	42	>25%	26	40	16	33	7
[11]	Guo 2004	2004	60	21.8	17.6	>5%	20	46	2	14	6
[12]	Li 2006	2006	56	18	47	≥10%	23	30	7	26	6
[13]	Uchibori 2006	2006	47	25.6	43.3	>10%	15	41	2	6	8
[14]	Zhou 2015	2015	48	12.4	24	>5%	8	34	1	14	6

Table 2

Detailed scores of included studies according to NOS scale.

Reference	Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at the start of the study	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	NOS score
[10]	Gong 2020	*	0	*	*	*	*	*	*	7
[11]	Guo 2004	*	0	*	*	0	*	*	*	6
[12]	Li 2006	0	0	*	*	*	*	*	*	6
[13]	Uchibori 2006	*	*	*	*	*	*	*	*	8
[14]	Zhou 2015	*	0	*	*	0	*	*	*	6

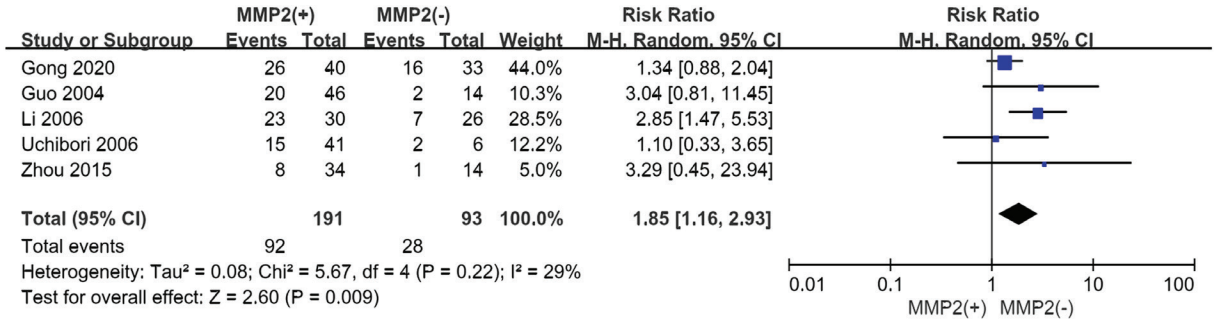

Fig. 2. Expression of MMP-2 and recurrence and metastasis rate of OS patients.

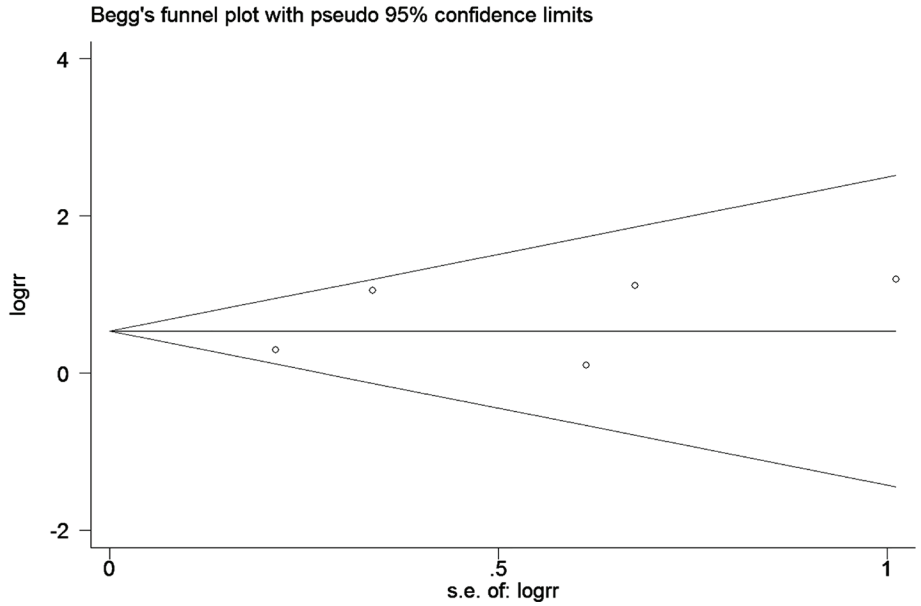

Fig. 3. Funnel plot for the publication bias.

the malignant phenotype of tumors [19]. Previous meta-analysis has suggested that MMP-2 overexpression has a close association with poor prognosis of ovarian cancer, non-small cell lung cancer, and gastric cancer [20-22]. Therefore, we conducted a meta-analysis to estimate the relevance between MMP-2 expression and OS recurrence or metastasis rate.

Five published studies were finally included (Fig. 1). Our results suggested that the MMP-2 overexpression predicted the higher recurrence and metastasis rate and poorer survival of osteosarcoma patients (RR=1.90, 95%CI:1.35-2.67, P<0.01) (Fig. 2). Considering that only five studies were included, subgroup analysis was abandoned.

A sensitivity analysis was then conducted by removing individual studies sequentially to appraise our results' stability. The pooled RR was stable since the elimination of any single study had no significant influence on it. The Begg funnel plot and Egger's test results have shown that there was no obvious publication bias in the research. All the above suggested that MMP-2 could be a potential prognostic biomarker for OS.

However, there are still some shortcomings in our meta-analysis. Only 284 cases (191 positives and 93 negative cases) were

included in the study. A relatively small sample size will inevitably lead to random errors, sample bias, and a decrease in the universality of our conclusion. At present, there has been no unified critical value to delimit the positive/negative expression of MMP-2, and there might be some bias since only papers written in Chinese or English were incorporated into our research. Although there is no obvious publication bias, there may still be potential publication bias in this meta-analysis since studies with significant results are more possibly to be published. In addition, a larger sample size and more studies are needed for subgroup analysis in terms of age, gender, tumor location, and treatment methods to obtain more general and detailed conclusions.

CONCLUSIONS

In conclusion, overexpression of MMP-2 predicts higher recurrence and metastasis rates and lower disease-free survival rates. MMP-2 has the potential of a prognostic biomarker of osteosarcoma. Nevertheless, more randomized studies with more samples are necessary to obtain a more solid evaluation of the prognostic value of MMP-2 for OS patients.

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Conflict of interest

None to declare.

Authors' ORCID Number

- Tianshu Gao: 0000-0002-5524-0234
- Zhenting Wang: 0000-0001-7329-1505
- Yi Liu: 0000-0003-0350-9008

Authors contribution

TG and ZW performed this study and drafted this manuscript. YL designed this study and significantly revised this manuscript. TG and ZW contributed equally to this study and should both be considered as first authors. All authors have approved the submission and publication of this manuscript.

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